

## Research on Smoking and Lung Cancer: A Landmark in the History of Chronic Disease Epidemiology

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This paper describes the history of the epidemiologic research on lung cancer prior to 1970 and its effect on chronic disease epidemiology. In the 1930s, epidemiology was largely concerned with acute infectious diseases. As the evidence grew that the incidence of lung cancer was increasing among men, however, epidemiologists undertook research into the etiology of the disease. In 1950, Doll and Hill, in England, and Wynder and Graham, in the United States, published substantial case-control studies that implicated the use of tobacco as a major risk factor for the disease. A controversy developed over the credibility of this finding and was increased in 1954 when a cohort study by Doll and Hill and another by Hammond and Horn each gave estimates that the risk of lung cancer was greatly increased among smokers relative to the risk among comparable non-smokers. An account is given of the disputes surrounding these and related studies. The controversy had a stimulating effect in fostering the developing discipline of chronic disease and epidemiology.

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Wade Hampton Frost, the first profession of epidemiology in the United States, described epidemiology in 1926 as concerned largely with the mass phenomena of infectious disease [1]. He did point out, however, that the limits of the discipline had become somewhat vague. It was customary to include in epidemiology the study of infections which were not characterized by distinctive epidemics, since these diseases had much in common with traditional epidemic diseases. He did not specifically include the effects of famine, which, on account of its role in dramatic depopulation, had often been linked with pestilence, but he did include a food deficiency disease, scurvy, and he also included goiter, which, like the others, could be profitably considered, in relation to the population at risk, a characteristic epidemiologic concept.

In the nineteen thirties, epidemiology was still concerned almost entirely with acute infectious diseases. Chronic diseases were becoming more important in the health field as a whole, however, partly in a relative sense because of the control of many infections, but also, to some extent, because of an increase in the incidence rate of certain chronic diseases. J.N. Morris, writing about British mortality data on middle-aged men, noted that as early as the 1920s death rates from coronary heart disease and lung cancer in men had been increasing. In a later part of his book he referred to these diseases as causing modern epidemics [2]. They showed a sustained, rather than an episodic, increase, less dramatic than a classic epidemic, but, like the latter, they invited attention by reason of the number of people affected.

A few small-scale epidemiologic investigations of the etiology of chronic disease had already been undertaken by the thirties. The rising interest in the field is illustrated by

the sustained cooperative efforts which were mounted at that period to gather data on the natural history of cancer. In 1935, the Connecticut State Legislature authorized a population-based cancer registry [3]. Two years later the National Cancer Institute was founded in the United States, and the first of three national cancer surveys, the Ten-City Survey, was organized [4]. In Denmark, a cancer registry covering the whole population was set up in 1942 [5]. These major undertakings were not restricted to research objectives, but the data obtained have served this purpose well.

What was still lacking in epidemiology at this time, however, was the successful completion of a major investigation of the etiology of a chronic disease. In the late forties, two large programs of epidemiologic research in chronic disease developed in response to the challenge of rising morbidity and mortality rates: research on smoking and lung cancer, carried out through several individual projects, and the Framingham study of cardiovascular disease, another comprehensive program of research. The objective of the present article is to describe the history of the research on lung cancer, briefly prior to 1950, and in greater detail for the more eventful period of 1950 to 1970, and to illustrate the stimulating effect of this research on the development of chronic disease epidemiology.

#### WAS LUNG CANCER INCREASING IN FREQUENCY? CONTROVERSY PRIOR TO 1950s

In the early part of this century, primary carcinoma of the lung was, according to Adler, "among the rarest forms of disease" [6]; a similar statement had been made by Bland-Sutton in 1903 [7]. By the 1930s, some evidence had been obtained that the incidence of lung cancer among males was increasing. The evidence came from three sources: official mortality statistics, pathologists' reports of autopsy findings, and the observations of physicians who specialized in the treatment of lung disease. The view that the disease was increasing provided a stimulus to search for a plausible cause, which, if the increase were as rapid and as widespread as it seemed, might well prove to be a changing environmental factor. Several such factors were suggested: one was the use of tobacco, and others included exposure to pollutants such as automobile exhaust, industrial pollution, smoke from domestic fires, and tars that were used in road construction. Non-environmental factors included late sequelae of influenza or tuberculosis.

Speculation about these factors continued, but there was also much criticism of the view that the reported increase in lung cancer was credible. These criticisms led to debate throughout the forties and early fifties. An editorial in the *British Medical Journal* in 1942 stated "It is doubtful whether the higher incidence of cancer of the lung observed in recent years is real or only apparent" [8]. Factors which were listed as likely to be responsible for an artificial increase were better diagnosis of the disease and increased longevity of the population.

The Medical Research Council of Great Britain in its report covering the years 1948–50 drew attention to the very great increase in the death rate from lung cancer in the previous 25 years, but conceded that "the increase may, of course, be only apparent" [9]. Its hedged conclusion was that it was reasonable to assume that the increase was partly real.

An indication of a developing consensus may be seen around 1950: Steiner, in 1950, reversed the opinion he previously held, that the reported increase was an artifact [10], and Clemmeson did likewise in 1954 [11], in the light of experience obtained after he

and Buck had reached a contrary conclusion earlier [12]. The in-house comments of the *British Medical Journal* also showed a change of emphasis from the editorial of 1942. A writer of the answers-to-correspondents column of 1948 stated without qualification that cancer of the lung had increased in frequency [13], and an editorial writer in 1950, impressed by substantial increases in proportionate mortality, noted that in Britain, in 1920, 1.5 percent of cancer deaths in men were due to cancer of the lung, and that this proportion increased to 19.7 percent in 1947 [14]. The writer added that similar changes had occurred in the United States, Australia, Switzerland, and Denmark.

In 1952, *Lancet* reported in an account of death rates, "Few trends are more dramatic than the rise during the last 30 years in the notified death rate from cancer of the lung. There is little doubt that the increase is both real and numerically important" [15].

The incidence rate of lung cancer as recorded by population-based cancer registries was greater in the forties than in the thirties and greater in the fifties than in the forties. It was this increase that made the phenomenon obvious to most observers. Clemmeson, director of the Danish Cancer Registry, wrote in 1954 that the rise was doubtful up until 1930, but "the disease is now increasing on a pandemic scale" [16]. The rapidity of the increase is illustrated by the following age-adjusted incidence rates per thousand males per year for Connecticut [17]:

Period	1935–39	1940–44	1945–49	1950–54
Rate	9.7	13.0	20.6	31.1

The successive five-year percentage increases were 34 percent, 58 percent, and 51 percent. The changes recorded in Connecticut and elsewhere were too substantial to be reasonably accounted for by underdiagnosis in the past. Doll has pointed out that if the lung cancer death rates of the early fifties in Britain had applied at the turn of the century, than 95 percent of fatal cases at that earlier time must have been wrongly reported on the death certificate [18].

During the late forties and the fifties, improved methods of diagnosis had become generally established. Physicians were assisted by the greater use of bronchoscopy and by the use of antibiotics to uncover an underlying malignancy in persons with pneumonia, and the population registries benefited from the higher quality of the data they received. This change is shown by data from the Connecticut Cancer Registry on the incidence of cancer of the trachea, bronchus, and lung over the period 1935–1954 [19]. The percentage of newly diagnosed males on whom the diagnosis had been confirmed by histologic examination increased in this period from 44.8 to 68.4. In addition, the percentage of cases that were registered on the basis of death certificate only, that is, registered in the absence of clinical notes from a diagnostician, declined from 32.2 to 16.6. These latter changes are affected by changes in survivorship, but they also reflect the improvement in the quality of the data that were registered.

The suggestion made by Burch in 1976 that there was underdiagnosis in the early years, followed by overdiagnosis as awareness of the disease was enhanced [20], though probably correct in qualitative terms, is implausible as a full explanation of the reported increase. By 1976, at the Connecticut Cancer Registry, only 1 percent of the cases of lung cancer were reported through death certificate alone, and only 12 percent lacked histological confirmation, but at this time the incidence rate of lung cancer was still increasing [21]. These facts undercut the claim that the reported increase in lung

cancer at this period was based on false-positive diagnoses. In 1954, a group of cigarette manufacturers in the United States made a statement acknowledging “the increased incidence of cancer of the lung in recent years,” but denying that there was any proof that smoking was responsible [22].

There was a good reason for the early uncertainty about whether lung cancer had been increasing, since the opposing views were initially based to a large extent on mortality data, which had been obtained by different methods of study. On the one hand, pathologists were conscious of the detailed work necessary to establish a probable cause of death, and they distrusted cause-of-death statistics based on death certificates; Willis argued that only “fully proved necropsy records” were of value in studying the apparent secular increase in lung cancer [23]. On the other hand, students of population were aware of the selective factors that influence the sample on which autopsy data are based, and they emphasized that such samples, lacking a well-defined population at risk, do not give a reliable guide to population trends in mortality. Controversy about issues in science tends to be spirited when the participants come from different disciplines, each with its own canons of evidence [24].

#### CASE-CONTROL STUDIES: FINDINGS AND CRITICISM

It is easier to accept an empirical finding about a rising incidence of cancer if there is a reasonable explanation of why an increase might have occurred. In 1954, Clemmeson flatly asserted that it was due to the widespread addiction to smoking [25]. It is well known that the proportion of smokers, particularly cigarette smokers, in the population of Western countries increased substantially during the first half of this century. Initially “smokers” were rarely cigarette smokers, and Kenneth Grahame, in *The Wind in the Willows*, refers to the use of cigarettes when “one is not smoking” [26]. The Department of Agriculture has made estimates of the average annual consumption of tobacco products in the United States among persons aged 15 years and over, from 1900 to 1960. During this period the number of cigarettes marketed, per person, increased by a factor of about 80, from 50 to 3,900; the sale of pipe tobacco decreased from 1.6 to .6 pounds, and the number of cigars fell from 110 to 60, per person [27].

Doll has noted that it had been known long before 1950 that smoking could cause disease, but it was “not until 1950 that a large amount of data was obtained in a sufficiently representative and responsible way to lead more than a handful of people to believe that smoking might actually be responsible for causing a material amount of disease” [28]. The two case-control studies in 1950 that were not only large but also well conducted were by Wynder and Graham in the United States [29] and by Doll and Hill in England [30,31]. The former was based on 605 cases and the latter was enlarged in 1952 to include 1,465. At least seven smaller studies, in which an association between smoking and lung cancer was found, were carried out prior to, or during, 1950 [32], the earliest being the paper of Müller on 86 cases and 86 controls in 1939 [33]. On the basis of clinical impressions, Ochsner and DeBakey as early as 1941 expressed “a definite conviction that the increase of pulmonary carcinoma is due largely to the increase in smoking, particularly cigarette smoking” [34].

Case-control methods were not new to epidemiology in 1950. One of the earliest examples of such investigation, indeed, was a matched study by Lombard and Doering in 1928 [35], implicating pipe-smoking as a risk factor for oral cancer. The paper by Doll and Hill in 1950, however, set higher standards than were previously attained in case-control studies by taking into account, in the design or analysis, a range of

potentially relevant factors: the age, sex, urban or rural residence, and social class of the subject; occupational history; exposure to air pollutants; forms of domestic heating; the place of interview; interviewer bias; diagnostic bias; and the history of smoking, including, for those who had smoked, the age of starting and stopping, the amount smoked before the onset of illness, the main changes in smoking history, the maximum amount smoked, the practice in regard to inhaling, and the use of cigarettes or pipe. They considered various possible explanations of their findings, searching for possible causes of confounding. The *British Medical Journal* wrote a favorable review of the paper, stating that it was meticulous and carried serious implications [36]. The paper has been well described as the prototype of the case-control study [37].

There were many who cast doubt on the evidence that had been produced against tobacco. One correspondent wrote to *Lancet* in 1951: "The evidence is purely circumstantial; it is obtained from statistical evaluation of clinical material" [38]. Another wrote to the *British Medical Journal* in 1952, "The only known carcinogen in cigarettes is arsenic. Some cause other than, or additional to, the increase in cigarette consumption must be sought to explain the increase in bronchogenic cancer" [39]. This important criticism was echoed by a correspondent to the *British Medical Journal* in 1953 who wrote: "no carcinogen has been found in tobacco smoke, although its presence and ultimate recognition are implied" [40]. Other correspondents to the *British Medical Journal* in 1953 raised objections to incriminating tobacco: "the fact that non-smokers contract the disease proves that smoking can at most be an aggravating factor . . . not the basic cause of bronchogenic carcinoma" [41] and "there has been no increase in the incidence of cancer of the mouth, tongue or pharynx" [42].

Other critics conceded that there was an association between smoking and lung cancer but did not regard the connection as causal. In 1953, the Minister of Health stated in the British Parliament: "The Standing Advisory Committee on Cancer and Radiology and the Medical Research Council both advised me that the relationship [between smoking and lung cancer] is not necessarily causal" [43] and in the same year a paper on smoking and lung cancer included the assessment: "There is an association but the question of whether smoking causes cancer is still open" [44].

Many essentially repetitive case-control studies of smoking and lung cancer were to follow. The large number was due to the disturbing finding that a pleasant and popular habit was, in the long term, potentially lethal. Conviction that this was so did not come easily. There was still the possibility, even, many thought, the near certainty, of the eventual emergence of credible scientific opposition which could, indeed, be expected since the finding at issue was somewhat inconclusive technically and the risk factor had been present for many years without exciting suspicion. In this case also, the product under discussion, tobacco, was sufficiently important economically to ensure its adequate defense. In 1954, the American Tobacco Industry issued a statement expressing confidence that this defense would prevail: "[It] accepts an interest in people's health as a basic responsibility paramount to every other consideration in our business" but does not "believe that tobacco products are injurious to health" [45].

One important criticism of the finding of an association between smoking and lung cancer centered on the use of the case-control method. It was expressed strongly in 1954 by Hammond [46], who was convinced that the increase in the incidence of lung cancer was real, and the resulting problem a serious one, and who was at that very time conducting, with Horn, a study which was subsequently to play an important part in concluding that the smoking of cigarettes was the major etiologic factor. The only

virtue he found in the case-control method was that under favorable conditions it was quick and inexpensive. He referred to the difficulty of obtaining appropriate controls, and he considered that an investigator who believed that tobacco caused lung cancer could influence a case's response to the question on smoking history. He also referred to what became known as Berkson's bias, which is based on the unrepresentative nature of prevalent hospital populations when used to reflect relationships that apply in the community. Because of the defects of the case-control method, some statisticians, Hammond reported, "believe that it leads to erroneous conclusions more often than to correct." Thirty years later Doll noted that bias "in the opinion of many at the time was inherent in the case-control method" [47].

### COHORT STUDIES

This methodological criticism was met in part by the planning of studies in which the outcome was unknown at the time of enrollment of subjects, since the contrasting groups of subjects were smokers and non-smokers rather than cases of lung cancer and controls. This design was originally described as prospective and has come to be known as the prospective cohort design. The term "cohort" is used in demography to denote a group of people who have all experienced some event within a defined calendar period, for example, a birth cohort or a marriage cohort. The defining event in the cohort study of lung cancer is the presence or absence of exposure, in this case the exposure due to smoking cigarettes, and since the onset of exposure may vary widely in calendar time even within one age group, the meaning of the word "cohort" is being extended in this epidemiologic usage; enrollment in a study is not an event in the demographic sense.

The use of the cohort design to study an etiologic problem in non-infectious disease is an advance that resulted from the research on smoking. Cohort studies of other types had long been used. The cohort life table, for example, in which the proportion surviving from a birth cohort is traced year by year to the point of extinction, was used by Deparcieux as early as 1746 [48]. In the nineteen thirties, Wade Hampton Frost took the step of adapting life table methods to study the epidemiology of an infectious disease, tuberculosis, as revealed by the follow-up cases [49], and his work on this disease was continued by several students.

It is therefore understandable, in the light of this experience in handling data on cohorts, that Doll should write in 1964: "the prospective method of inquiry is in concept extremely simple" [50]. The practical difficulties in applying the method to epidemiologic problems of the type raised by cigarette smoking were nevertheless considerable. Cornfield, who was experienced both in research on smoking and in the design of epidemiologic studies, had written in 1951: "An investigation that involves selecting representative groups of those having, and [others] not having, a characteristic is expensive and time consuming . . . and is rarely if ever used" [51]. In the early fifties, these problems were overcome by Doll and Hill [52,53] and by Hammond and Horn [54,55,56] in their research on smoking, the former having a slight priority in date of publication. At about the same time, a related type of cohort study was described by Case and colleagues [57], one in which the cohort was identified at some point in the past, then followed to the present time by means of available records, and finally followed prospectively, during a period in which most of the outcome events occurred, to the end of the study. This procedure is the historical cohort type of study. The research by Case and colleagues on the causation of cancer of the bladder by dyestuff

intermediates was published in 1954, the same year as the Doll and Hill cohort study, and the two have been coupled as a landmark in the historical development of cancer epidemiology, and thus in the development of chronic disease epidemiology in general [58]. What is novel about their use of this method is its application to the study of the etiology of a non-infectious disease. Following these examples, similar cohort studies on a smaller scale have become routine [59]. When the acute stage of an infectious disease blends with chronic sequelae as in tuberculosis, it is clear that follow-up of the cohort affected is needed both for purposes of treatment and for progress in knowledge of the disease. When there is no such natural link between risk factor and resulting pathology, there is less encouragement to undertake a long and potentially expensive cohort study. The findings from the case-control studies of smoking, however, though challenging, had not convinced some whose judgment had to be respected, and the value of an independent method of studying the problem was obvious.

The first two cohort studies of the effects of smoking began soon after the case-control investigations ended. Doll and Hill sent out questionnaires to British physicians in October 1951 and obtained 40,000 usable responses. In early 1952, Hammond and Horn, of the American Cancer Society, began their questioning of 188,000 white males all in the age group 50 to 69. Within the same decade, four other large cohorts were enrolled in similar studies [60]. What is of interest in the outcome is the general concordance in findings between the cohort studies and between the cohort and the earlier case-control studies. It is true that in the British research the lung cancer death rate was substantially higher in the case-control than in the cohort study, but the former estimate involved some data that were obtained outside the study and was necessarily tentative.

The cohort studies verified the association between smoking and lung cancer and also found that the lung cancer death rate was substantially higher in cigarette smokers than in smokers who used pipes or cigars; that the strength of the association between smoking and lung cancer increased with the amount of smoking; that the association differed according to the histological type of tumor; and that those who renounced smoking had a lower death rate than otherwise comparable subjects who continued to smoke. An important additional finding of the type possible in cohort studies, which can monitor the outcome in several diseases, was that cigarette smoking is a risk factor for coronary heart disease. This finding was initially missed by the Framingham study of cardiovascular disease which, in 1950, had become oriented toward the study of risk factors. A 1957 paper from Framingham noted that Hammond and Horn, and Doll and Hill, had found an association between smoking and cardiovascular disease, but added that in the Framingham study "smoking habits were not notably associated with the development of new arteriosclerotic heart disease" [61]. New disease included angina as well as the fatal forms of disease studied by Hammond and Horn. A further analysis of the Framingham data, in which angina pectoris was treated separately, was made in 1959, and a weak but positive association with smoking was observed [62]. In 1962, data from Framingham were merged with those from a similar Albany study, and heavy smokers were estimated to have three times the risk of cardiovascular disease experienced by non-smokers [63]. It is likely that the person-years of exposure in the Framingham study were too small at the time of the early reports to provide convincing evidence of the effect of smoking on cardiovascular disease. Hammond and

Horn, in particular, must be given credit for producing data which convincingly established cigarette smoking as a risk factor for coronary heart disease.

#### FURTHER DISCUSSION OF EVIDENCE: RENEWAL OF CONTROVERSY

A third substantial cohort study of smoking, based on United States veterans, was published in 1959 [64]. The fifties and early sixties may be considered to be the period in which the epidemiologic data in favor of the etiologic role of tobacco in lung cancer were marshalled, and opinion against smoking began to crystallize. In 1957, the Medical Research Council in Britain issued a strong statement in which it claimed that the occurrence of most of the lung cancer cases was associated with the use of tobacco, particularly in the form of cigarettes, and the most reasonable interpretation was that tobacco was the direct cause of the cancer [65].

The Surgeon General of the United States took a similar position: "The weight of the evidence is increasingly pointed in one direction: that excess smoking is one of the causative factors in lung cancer" [66]. The definitive results of the Doll and Hill cohort study and the Hammond-Horn study were available at that time. These papers and the discussion they stimulated helped to set off a new period of controversy which was to last for at least another decade. Following the publication of the statement by the Medical Research Council in Great Britain in 1957, the Minister of Health, Dr. Hill, was asked the following Parliamentary Question: "Are there not strong grounds for thinking that the Medical Research Council has stuck out its neck much too far?" Dr. Hill replied: "The facts are clearly known. The case has been fully established" [67]. For him, the evidence against cigarettes in 1957 was beyond the reach of successful contradiction.

In this same year, however, Compton Mackenzie published his book, *Sublime Tobacco* [68]. He stated that he wrote it "as a token of gratitude for the immense benefit I have received from tobacco, and in complete certainty that I have not derived from it the slightest harm." A reviewer for *Lancet* praised the graceful and elegant style, but also claimed that the book was dangerous, perhaps immoral [69].

In 1956, the *British Medical Journal* published the answers given by Doll and Hill to 31 questions it had submitted to them about smoking and lung cancer [70]. It is an indication of the journal's assessment of reader interest that so many facets were found on which medical practitioners might require information or reassurance. Five years later, the *New England Journal of Medicine* carried out a similar policy, in its own way, by publishing details of a debate on the same subject between E.L. Wynder [71] and C.C. Little [72].

In 1959, the Surgeon General of the United States, Dr. Leroy E. Burney, issued a statement which reviewed the available data and concluded: "The weight of evidence at present implicates smoking as the principal etiological factor in the increased incidence of lung cancer" [73]. What the Surgeon General had referred to two years previously as "one of the causative factors" had become "the principal etiological factor." The editor of the *Journal of the American Medical Association*, Dr. Talbot, published the statement and added in an editorial "a number of authorities . . . do not agree with his conclusion" [74]. Dr. Talbot argued that there was insufficient evidence to resolve the issue. His advice was that physicians should watch the situation closely, keeping courant of the facts, and advise patients on the basis of appraisal of the facts. This recommendation drew a response from the editor of the *New England Journal of*

*Medicine*, who saw the cautious phrasing of Dr. Talbot's statement as encouraging indecisiveness which could no longer be justified; this encouragement, he wrote, might have been unintentional, but he made his own position clear by strongly endorsing Dr. Burney's views [75]. More detailed and stronger statements were to follow from the Royal College of Physicians of London in 1962 [76] and from the Advisory Committee to the United States Surgeon General in 1964 [77]. In response to the Surgeon General's Report, the American Medical Association agreed that cigarette smoking was a serious health hazard [78].

#### CRITICISMS BY JOSEPH BERKSON

Since the epidemiologic evidence against smoking, like many of the findings of chronic disease epidemiology, draws on statistical analyses, great interest was roused by the fact that two well-known statisticians, Joseph Berkson and R.A. Fisher, did not accept the claim that smoking caused lung cancer.

Berkson was impressed by the large number of diseases that Hammond and Horn showed to differ significantly in frequency between smokers and non-smokers. The list, expressed in the rubrics used by the International Classification of Causes of Death, included not only cancer of the lung, although the risk of smokers relative to non-smokers for this condition was extraordinarily high, but also such disease outcomes as cancer of the bladder, coronary heart disease, cardiovascular disease, aortic aneurysm, pneumonia and influenza, and gastric ulcer and duodenal ulcer. Berkson wrote: "We have here a great deal more than was bargained for, and most of it without relation to what it was intended to explain, the observed rise in death rate from cancer of the lung" [79]. Berkson's argument had been commonly used in infectious disease epidemiology and had been recommended, with reservation, when one wished to infer causality in studying the etiology of chronic diseases. Specificity of action is a principle which works well in studies made at the molecular level. If the unit of study is the whole organism, however, the principle of specificity has limited usefulness, although it may sometimes warn of false-positive associations. The absorption of even a single substance, let alone the complex smoke from tobacco, may affect many organs or systems.

Berkson advanced another general argument which was repeated in various ways in the debate about cigarettes. "The definitive investigations," he wrote, "must come from the biologic sciences, pathology, pharmacology, chemistry and so forth . . . we will not really know whether smoking causes cancer, till we know at least something in a precise way about how it causes cancer" [80].

Many critics either agreed with the phrase "not really know" or, at any rate, considered that evidence at a more analytic biological level was desirable. They made Berkson's argument more pointed by asking once again for evidence of the precise substance that constituted the active principle of tobacco, and demanding the experimental production of cancer by this substance.

In the fifties, even before Berkson had stated his view, a vigorous effort was made to isolate chemical carcinogens from tobacco. The model for this was the isolation from coal tar in 1932 of a very active carcinogen, 3,4-benzopyrene [81], which was presumably the main agent responsible for chimney sweepers' cancer. There were numerous examples from biomedical research of the success which could ensue when a crude biological product was fractionated to isolate the active component. Many years previously, John Shaw Billings had drawn attention to the error of those who had failed

to follow this principle in the investigation of "milk sickness." He noted that he had read 110 articles on the subject, and he then complained: "It has been said to be caused by certain plants, yet no scientific experiments have been made on the effects of these plants. No attempt has been made to produce the disease . . . by the use of suspected plants, or better, by the use of an extract containing the active principles" [82].

In the case of tobacco the efforts were made, but the direct results from this strategy were minimal. In 1958, by which time there was substantial epidemiologic evidence on smoking as a risk factor for lung cancer, the *British Medical Journal* commented as follows on this evidence: "The fact that experimental work has not provided complete and irrefutable proof has tended to hinder its wholehearted acceptance" [83]. A representative of the tobacco industry described this objection more forcefully, by stating that the search for chemical carcinogens in tobacco "has now been continued so long in the hands of so many able investigators and with such meager results that many scientists no longer believe it likely that tobacco smoke exerts any significant effect as a direct or specific carcinogen for human tissues" [84]. In 1962, *Lancet* summarized the results of the chemical analysis of tobacco products by noting "no carcinogen has been found in adequate concentration in tobacco smoke; no genuine lung cancers have been produced experimentally" [85]. This observation engendered "a slight nagging uncertainty about the evidence . . . we must have our carcinogen and our experimental verification." These requirements can be recognized as a rephrasing of part of the Henle-Koch postulates so as to apply them to a chronic disease.

In this climate of opinion, it was possible to accept the idea that the epidemiologic evidence against tobacco was, in general, correct but that the magnitude of the effect had been overestimated, owing to various uncertainties in the data. If this were the case, it might be possible to modify tobacco slightly by removing some injurious constituents without altering to a great extent either its composition or its appeal. In 1961, the Tobacco Research Council, which was funded by cigarette manufacturers, set up its own laboratories to pinpoint any specific chemicals suspected of being carcinogens and to "provide a basis for formulating less carcinogenic smoking materials" [86]. The goal was to produce a safer cigarette, but no progress was made on which constituents should be removed from tobacco. Berkson's request for research on the active principle was appropriate, but there was no early explanation of how tobacco produced lung cancer, the evidence for which many found compelling. There may in fact be no single active principle in this case; many diseases depend on the interaction of two or more risk factors, and in 1955 Woodhouse and Hamer suggested that cigarette smoke might be a co-carcinogen [87].

A further argument used by Berkson is of general interest even though it was rapidly countered by ongoing data. He noted that the death rate among the subjects enrolled in the cohort studies, according to the early publications, was low in relation to general population death rates, and he drew the inference that the sampling used was so biased that conclusions based on it would be unreliable [88]. An inference made from an ongoing study in the early stages, however, becomes a prediction for later findings, and the low mortality that Berkson observed initially did not last. The death rate subsequently rose among smokers and non-smokers, but the differential between these two groups was consistently maintained. Actuaries are familiar with a phenomenon known as the wearing off of the effects of medical selection in which some applicants for insurance are required to pay penalty rates initially, but the survivors of the group are no longer penalized after three or four years. What wore off in the cohort studies was

the advantage of above-average health rather than the handicap of morbidity, but the mechanism was presumably similar in the two cases.

### CRITICISMS BY R.A. FISHER

R.A. Fisher's work on smoking and lung cancer preceded Berkson's and differed in its thrust; it was published as a booklet in 1959 [89]. In studying the data on smoking, Fisher [90] emphasized a finding from the Doll-Hill case-control investigation on the effect of inhalation of the smoke. The proportion of smokers who stated that they inhaled was 65 percent among the cases and, surprisingly, higher, 67 percent among the controls. The editorial accompanying the paper in the *British Medical Journal* in 1950 had commented on this unexpected result [91]. Cornfield and his colleagues stated in 1959: "It must be admitted that there is no clear explanation of the contradiction posed" [92]. Fisher pursued the matter to the point of obtaining original data from Doll and Hill and publishing it in his booklet. Smokers among the cases and among the controls were classified by whether they inhaled when smoking, and the data were presented in five subgroups, according to the amount smoked per day. In four of the five groups, the percentage of inhalers among the controls was higher than among the cases. These data played an important part in leading Fisher to doubt that tobacco was a carcinogen. It has subsequently appeared that light smokers deposit little particulate matter on the susceptible part of the bronchi unless they inhale. Heavy smokers, on the other hand, who tend to inhale deeply, deposit less when they inhale than when they do not, since in the former case the smoke moves rapidly to the deeper portions of the lungs [93]. The issue deserved the discussion that Fisher prompted and may occasion more.

Fisher noted that the original hypothesis about the effect of tobacco became an hypothesis about the effect of cigarette tobacco. Originally Doll and Hill had treated an ounce of pipe tobacco as roughly equivalent to 28 cigarettes. Fisher regarded them as having modified their hypothesis to interpret the very study that was designed to test it. This was, he wrote, "the making of an assumption which might be true, and indeed, might not be true, but which, if true, would help to explain what is otherwise inexplicable" [94]. The force of this objection depended on its timing, since the issue is whether the assumption is true or not. As more and more investigators failed to negate it, it has become an accepted view of a difference between the use of pipe tobacco and cigarette tobacco.

In 1957, Fisher followed others in arguing that the male-to-female ratio in the incident cases of lung cancer was inconsistent with the male-to-female ratio of smokers [95]. The findings were correct when based on the ratios seen in the data available for a restricted period. Research on lung cancer, however, has to take into account the long latent period between exposure and disease, so that the proportion of incident cases today depends on the proportion whose exposure began many years ago, and, if the proportion exposed is increasing or decreasing over time, the ratio of cases to exposed, based on current data, is misleading. There are many examples of a long interval between an initial exposure and the final disease, including several classic cases in infectious disease epidemiology. The association of smoking and lung cancer is not unique either in the length of the latent period or in the resulting difficulties in the study of the etiology.

Fisher initially conceded that a good *prima facie* case had been made out against smoking [96] but his summarizing complaint was that the attitude toward research on

lung cancer in the fifties had been marked by “excessive confidence that the solution has already been found” [97], and he called for continued research, particularly of the type that did not simply repeat designs that had already been exploited repetitively. He cited the association between blood group A, an inherited factor, and cancer of the stomach, and proposed two new research projects based on the theory, commonly known as the constitutional theory, that “cigarette smoking and lung cancer . . . are both influenced by a common cause . . . the individual genotype” [98]. He was almost alone among the major critics in advancing, and indeed pursuing, a proposal for gathering further empirical data.

The first project was a population survey in which differences in genotype as assessed by taste testing, secretor status, and blood grouping, would be related to smoking habit. A simple version of such a study had been completed by Fisher and Vaughan in 1939. Working in an English town, close to Wales, they had identified Welsh migrants by their surname, and shown by ABO blood grouping that the persons so identified differed in genotype from the English majority [99]. If genotype differences were associated with the subdivision into smoking classes, this finding would at least encourage further work on the constitutional hypothesis. The proposal for a population survey of genotypes does not seem to have been taken up, though other differences between smokers and non-smokers were studied in detail.

Fisher’s second proposal called for research on twins and was designed to show whether there was greater concordance in smoking habit between the members of monozygotic pairs than there was between members of dizygotic pairs. Some evidence that the monozygotes were more concordant was obtained during Fisher’s lifetime, and was based in part on twins who had been reared in different households [100]. The numbers involved were too small to yield useful information on morbidity or mortality of the twins. Fisher’s death occurred in 1962 before the controversy about the effects of smoking had abated, indeed before the controversy among the general public had reached a peak. Unlike Berkson, he did not publish a statement concerning the cohort studies.

The constitutional hypothesis was strongly supported by Brownlee in 1965 in an unfavorable review of the Surgeon General’s Report on Smoking and Health [101]. Writing about the hypothesis some years after it had been introduced, Mantel stated that it had been difficult to reject [102]. A modified form of the hypothesis in which the interaction between genotype and tobacco is treated as a risk factor remains credible. The constitutional hypothesis was incompatible, however, in its original form, with the speed with which lung cancer had increased during this century; Burch, who has continued to support the constitutional theory, denied that a substantial increase in lung cancer had, in fact occurred [103]. Since the genotype postulated by the constitutional theory has not been identified by a phenotypic expression, any epidemiologic research on it has had to be carried out without knowing who had the hypothesized genotype and who did not.

#### BEGINNING LITERATURE ON METHODOLOGY OF CHRONIC DISEASE EPIDEMIOLOGY

The cohort and case-control studies of smoking, and the controversy they generated, were of prime interest to those concerned with lung cancer. They also had a wider influence since they directed attention to methods of conducting epidemiologic studies of the etiology of chronic disease. In the course of a few years around the end of the

fifties, Lilienfeld [104], Sartwell [105], and a joint team consisting of Yerushalmy and Palmer [106] wrote about methodology for the new discipline. Lilienfeld, Sartwell, and Palmer had contributed to research on infectious disease epidemiology, and they used Koch's postulates, modified by their experience with chronic diseases, to provide a framework for the new methods; as Yerushalmy and Palmer expressed it in 1959: "It is the purpose of this paper to develop an elementary parallel between investigation of etiological factors in certain chronic diseases and those of bacterial diseases." Yerushalmy and Palmer were ambivalent about the role of smoking in lung cancer. Their ambivalence did not sit well with some colleagues to whom they showed a draft of their paper and, in a footnote responding to the "comments by several very competent persons" they noted that their statements on smoking and lung cancer were made only to illustrate methodology and not to express a judgment on the relative value of such other evidence as might bear on the question.

While the appropriate methods for the study of chronic disease epidemiology were being discussed, improvements in these methods were being developed. Three publications in the fifties were especially important in relation to lung cancer and to chronic disease epidemiology in general.

In 1951, Cornfield showed that the estimates from case-control studies were much more informative than had been previously supposed [107]. In the case of smoking and lung cancer, for example, the obvious estimates are the proportions of smokers among the cases and also among the controls. These may readily be converted, however, to an estimate which is more illuminating, namely the risk of lung cancer among smokers relative to the risk among non-smokers. The higher this relative risk, the less likely is it that an apparent effect of smoking can be explained as an artifact due to confounding. This likelihood was the basis of one of the arguments used by Cornfield in criticizing Berkson's dependence on risk differences, rather than risk ratios, in judging the effect of smoking on the etiology of lung cancer. Cairns was responding to the same logic as Cornfield when he later wrote that cancer of the lung was so strongly dependent on smoking that the causal connection could be identified without the need to understand the underlying mechanism of carcinogenesis [108].

A second publication, issued in 1959, was a thorough exposition of the evidence regarding smoking as a cause of lung cancer. It included an appendix, which is probably due to Cornfield [109], in which new methodological issues were presented. An example of these was a quantitative treatment of an aspect of confounding. Suppose smokers and non-smokers are compared in regard to the occurrence of lung cancer, and it is found that the risk among those who smoke, relative to the risk among those who do not smoke, is  $r$ . Then if cigarette smoking as such is without influence on the development of lung cancer, and its apparent effect is simply due to confounding, say by a genotype which is more common in smokers than in non-smokers, the proportion of smokers with this genotype must be at least  $r$  times as great as the proportion of non-smokers with the genotype. This circumstance puts limits on the extent to which speculative suggestions can be offered without supporting evidence as a reason for rejecting a data-based finding in an epidemiologic study of etiology.

A third influential paper was written by Mantel and Haenszel, who in 1958 provided a systematic account of the design and analysis of case-control studies [110]. They gave an exact method of combining the evidence obtained from several strata about the presence of an association between a risk factor and a disease, and they introduced an

overall estimate of the ratio of the odds in favor of exposure among cases relative to the corresponding odds among controls.

The methods that flowed from the work on smoking soon became common in chronic disease epidemiology which, as Vandembroucke has written, was "heavily rooted in the smoking-lung cancer controversy" [111]. By the mid-fifties, the major epidemiologic research that had been published on the etiology of a chronic disease was the research on smoking. It not only provided an account of how such epidemiologic studies could be conducted and analyzed, but it also exhibited successful examples.

### EFFECT OF EPIDEMIOLOGIC STUDIES OF LUNG CANCER

Innovative work by epidemiologic methods on smoking and lung cancer subsided in the seventies; the topic, at the epidemiologic level, was becoming exhausted. *Lancet* stated in an editorial: "In the fifties the medical profession was equivocal in its attitude to smoking; in 1970 the profession is more or less united in the view that cigarette smoking, in particular, endangers health" [112].

In 1970, scientists were not ready to do what Berkson and others had proposed as a further test of the smoking hypothesis: namely, to identify the mechanism that leads to lung cancer. An editorial in *Nature* in 1984 stated: "It will be time enough to talk about causes of lung cancer, when mechanisms have been worked out . . . [It] will require more molecular biology and cell biology . . . better understanding of the process of differentiation and physiology of homeostasis . . . . People who smoke cigarettes are more likely than others to develop cancer. The habit of smoking is thus . . . a cause of cancer . . . [but] not a first cause . . . that distinction no doubt lies with a group of chemicals not yet conclusively demonstrated" [113].

The first cause, the very first cause, of lung cancer is elusive and the search for it may be never-ending. At any given time, there is also the issue of whether knowledge obtained by that time can be usefully applied. The epidemiologic evidence against smoking has justified a preventive campaign which has had success in spite of the heavy odds against it. The success is modest in relative terms but beneficial to many people. The findings laid the basis for a method of avoiding the most common form of lung cancer and, by adding tobacco to the list of controllable risk factors, they expanded preventive oncology far beyond its established role in reducing occupational carcinogenesis and skin cancer.

During the period covered by this study, two of the events that shaped the way in which chronic disease epidemiology emerged as a discipline were the dramatic increase in lung cancer and the opposition to the claim that cigarette smoking was a major cause of the disease.

The increase in lung cancer, unexpected and, in the short term, unexplained, created the need for etiologic research. In response to this need the case-control study was raised to a new level of quality by Doll and Hill. The method is well adapted to etiologic studies whenever the risk factor can be assessed by taking a subject's history, and it is especially effective, relative to other methods, when the disease has a long latent period, as is typical of chronic diseases.

The findings from the case-control studies were too important, too unpalatable, and too surprising to be accepted without extensive criticism, and the reaction to this criticism had a marked effect on epidemiology. One response was to design an etiologic cohort investigation, which demonstrated that a behavioral risk factor could be studied successfully in a prospective manner. Another was to stimulate interest in improving

the statistical methods by which epidemiologists analyzed data on the etiology of chronic disease. Work on an important problem, pursued over many years in the face of informed opposition, is likely to lead to methodological advances, and this consequence has been true of research on smoking. Some of these advances came from the pioneer investigators and some from those who were stimulated by a worthwhile problem. In the long run, these contributions to methodology may rank in significance with the substantive findings from the investigation.

Bringing the chronic diseases within the scope of epidemiology has stimulated two changes in that discipline. The first is the widening of the search for etiologic agents in diseases which had previously been thought of, in large part, as due to degenerative changes. The principal, though not the sole, agent in the case of infectious diseases is the organism which acts as the risk factor, and the investigation of the characteristics and transmission of this agent imparts a special focus to the relevant research. The organism is a necessary factor in causation of the disease even if it is not a sufficient factor. In chronic disease the etiologic agent may be an infection, but the disease may also be due to such factors as diet, behavioral characteristics, occupation, family life, environmental pollution, inherited abnormality, therapeutic misadventure, or several factors combined.

A second change which is a consequence of the first is the need for emphasis on certain knowledge and skills used in research on chronic disease epidemiology. This development has led to a specialized literature.

Two publications by Doll and Hill, one by Hammond and Horn, and one by Wynder and Graham [114] played a major part in the early fifties in arousing public and professional interest in the relation of smoking to lung cancer. In all four instances the papers were published in general medical journals. These very papers, however, were influential in fostering a discipline of chronic disease epidemiology which required new journals or at least modifications of old ones. The *British Journal of Preventive and Social Medicine* and the *Journal of Chronic Diseases* began publication in 1946 and 1947, respectively, but, although they each published epidemiologic papers, that was not their sole or even primary function.

In 1965 the *American Journal of Hygiene*, which had long been an important journal for the publication of papers on the epidemiology of infectious diseases, signalled a change of emphasis by altering its name to the *American Journal of Epidemiology*. It maintained its interest in infectious diseases but it also rapidly became an important medium for the publication of papers on chronic disease epidemiology. This same shift of emphasis occurred in other countries, and in 1972 the *International Journal of Epidemiology* began publication with similar objectives.

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